REMARKS

Claims 49-61 and 63-69 are currently pending. Claim 49 has been amended to point out more clearly that the method can be used to treat ischemic myocardial tissue. Support can be found at least at page 7 line 30 to page 8 line 8, and page 16 lines 9-21. Claim 50 has been amended to help improve claim clarity. Claim 61 has been amended to incorporate specific embodiments of claim 62. Support can be found at least at page 21 line 31 to page 22 line 7. Claim 62 has been canceled. Claims 1-48 were canceled in the preliminary amendment filed on July 16, 2004. No new matter has been added by virtue of the amendments.

35 U.S.C. §112 first paragraph (written description)

Claims 49-66 stand rejected as not complying with the written desrcription requirement. According to the Office, "[t]here is literally no written support" for a method that induces blood vessel growth in myocardial tissue of a mammal in need of such treatment. Action at pg. 2. To the extent the pending claims have been examined under this standard, the rejection cannot stand. Respectfully it is improper and should be withdrawn.

In support, Applicants point to the Guidelines for Examination of Patent Applications Under 35 USC §112, 1¶, "Written Description Requirement (hereinafter "Guidelines"):

> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the now claimed invention (citing *Vas-Cath, Inc.* 935 F.2d at 1563-64, 19USPQ2d at 1117).

See the Federal Register, Vol. 66, pp. 1099-1111, part IB at pg. 1105. See also MPEP 2163.02, for instance.

Thus, the correct inquiry is to confirm that Applicant was in possession of the subject matter claimed as of his filing date. An allegation that "there is literally no written support" for a claimed method is simply not an appropriate test. The Guidelines are flexible and provide several ways in which possession of the claimed invention can be demonstrated as of the application filing date.

Moreover, there is no statutory or other requirement that requires Applicant to provide literal written support to satisfy §112. See MPEP 2163.02, for example.

Having reviewed the proper framework for an inquiry under 112, first paragraph (written description), Applicants respond to the rejection as follows.

Applicants have amended claim 49 to make more explicit what was implicit in the claim as filed. In particular, claim 49 has been amended to point out more clearly that the method can be used to *treat ischemic myocardial tissue*.

The USPTO alleged that there is no written support for a colony stimulating factor (CSF) or an effective fragement thereof on grounds that such a factor "is not necessarily limited to G-CSF or M-CSF because it may encompass other proteins and peptides which can act on macrophages and are capable to modulate vascularization". Action at pg. 3.

In response, the Office is respectfully requested to clarify and provide support for the assertion that CSF may encompass other proteins and peptides that act on macrophages and are capable of modulating vascularization. Action at pg. 3. In the absence of such support, this ground of rejection is improper and cannot stand.

To respond further, Applicants note that the Office has already taken the position in U.S. Pat. No. 6,676,937 (by virtue of the allowance) that issued claims 22 and 39, for instance, fully satisfy the requirements of of 35 USC § 112. These claims, for instance, recite "colony stimulating factor (CSF)". Accordingly, there is no basis for the assertion that recitation of "colony stimulating factor" is somehow unsupported by the present case as filed.

On these grounds alone, reconsideration and withdrawal of the rejection are requested.

Applicants respectfully disagree with the assertion at pg. 3 of the Action that the specification:

> does not support a concept for a co-administration of a nucleic acid encoding at least one angiogenic protein or an effective fragement thereof with a colony stimulating factor (CSF) or an effective fragement thereof.

In response, Applicants have alread pointed to ample support in the prior response. Further support can be found at pg. 19, lines 10-24 of the application which discloses, among other things, that **administration of the vascularization modulating agent may be augmented by co-administering at least one angiogenic protein**. The angiogenic protein can be administered directly or nucleic acid encoding the mitogen may be used. Specification at pg. 19, lines 17-19. The specification broadly defines "vascularization modulating agent" at pgs. 4-5, bridging paragraph; pg. 21, lines 13-25, for instance, as including a variety of factors such as hematopoietic factors that increase EPC mobilization. In particular, SCF and specific colony stimulating factors (GM-CSF and C-CSF) are disclosed as illustrative vascularization modulating agents. At pg. 21, lines 13-25. Angiogenic proteins are defined at pg. 20, lines 12-26 as including colony stimulating factor (**CSF**), M-CSF, and GM-CSF.

Accordingly, and contrary to the position taken by the Office, there is abundant support in the application as filed for the concept of co-administering a nucleic acid encoding at least one angiogenic protein or an effective fragement thereof with a CSF or an effective fragment thereof.

The Office's concern regarding the recitation of "an anti-coagulant before, during or after administration of a nucleic acid encoding a least one angiogenic protein or an effective fragment thereof has been addressed. See amended claim 61.

On pg. 4 of the Action, the Office asserted that Applicants are not entitled to the filing date of provisional application 60/077,262 as filed on March 9, 1998. Applicants respectfully traverse.

Support for the administration of GM-CSF prior to treatment of the ischemic tissue with DNA encoding angiogenic proteins can be found at least at page 4, lines 4-6. Support for CSFs other than GM-CSF can be found in the description of the modification of GM-CSF protein, found at least at page 6, lines 4-15. Reconsideration of Applicants' priority claim is requested.

35 U.S.C. §103

Claims 49-66 stand rejected as being unpatentable over Isner (WO 97/14307) in view of Hammond et al. (USP 5,880,090). Applicants respectfully traverse.

As cited, Hammond provides methods for enhancing the endothelialization of a synthetic **prosthetic vascular graft** using certain cytokines such as G-CSF and GM-CSF. See col. 2, lines 39-49. As cited, the reference does not teach or suggest using the method to treat ishemic myocardial tissue, particularly along with injection of a nucleic acid encoding at least one angiogenic protein. As relied on, Isner does not specifiy using SCF or CSF to treat myocardial ischemia.

For these reasons alone, the Office has not established a prima facie case. Reconsideration and withdrawal of the rejection are requested.

Applicants respectfully disagree with the rejection on other grounds.

For instance, Hammond cites a 1997 publication by Asahara et al. that according to Hammond proposed that circulating CD34+ or Flk-1+ cells participate in the repair of ischemic tissues. Hammond, as relied on, is **nothing more than in invitation to experiment** with the circulating cells. It certainly does not disclose or suggest using those cells to treat ischemic myocardial tissue.

Moreover, claim 49 has been amended to recite a new step (a) relating to identifying suitable mammals. As cited, the combination of references do not include this step.

In view thereof, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 49-66 stand rejected as being unpatentable under 35 USC § 103 over Isner (WO 97/14307) in view of Bussolino et al. (*J. Clin. Invest.* 87: 986 1991). Applicants respectfully traverse.

As cited, Bussolino is said to teach use of particular CSFs to induce endothelial cells to proliferate and migrate *in vitro*. Applicants note that the reference provides for use of the CSFs in the rabbit cornea. However, nowhere does the reference teach or suggest use of the presently claimed invention to treat ischemic myocardial tissue.

For this reason alone it is submitted that the Office has not made a *prima facie* case.

In addition, Bussolino states that the effect of G-CSF on the rabbit eye was detectable but weak. Thus a worker in the field would have been especially dissuaded from using CSFs (and G-CSF in particular) to induce endothealization *in vivo*. Indeed, there would have been no motivation to combine Bussolino's use of the G-CSF with Isner's disclosure as cited by the Office.

Moreover, claim 49 has been amended to recite a new step (a) relating to identifying suitable mammals. As cited, the combination of references do not include this step.

Claims Rejections – Double Patenting

Claims 49-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No. 10/696,391. Applicants will address the issue once there is indication of allowable subject matter in this case.

Early consideration and allowance of the above-captioned application are respectfully requested. The USPTO is authorized to charge our deposit account **04-1104** for any fees needed to consider this submission.

Respectfully submitted,

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